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Oxycodone

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Abstract

Oxycodone has been in clinical use since 1917. Parenteral oxycodone was used mainly for the treatment of acute postoperative pain whereas combinations, for example, oxycodone and acetaminophen, were used for moderate pain. Since the introduction of controlled-release oxycodone, it has been used to manage cancer-related pain and chronic non-cancer-related pain problems. Controlled studies have been performed in postoperative pain, cancer pain, osteoarthritis-related pain, and neuropathic pain due to postherpetic neuralgia and diabetic neuropathy. The pharmacodynamic effects of oxycodone are typical of a µ-opioid agonist. Oxycodone closely resembles morphine but it has some distinct differences, particularly in its pharmacokinetic profile. Being an old drug, the basic pharmacology of oxycodone has been a neglected field of research.

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Key Words

Oxycodone, oxymorphone

Introduction

Oxycodone has been in clinical use since 1917.\(^1\) It has been administered to human beings intravenously (i.v.),\(^2,3\) intramuscularly (i.m.),\(^4\) intranasally (i.n.),\(^3\) subcutaneously (s.c.),\(^5\) rectally,\(^6\) epidurally,\(^7\) and orally using immediate-release solutions,\(^4,8–10\) and immediate- and controlled-release tablets.\(^11\) The transdermal route of administration has also been tested in animals.\(^12\)

Today oxycodone is mainly used as controlled-release tablets for chronic pain. The immediate-release solution and tablets are used for acute pain or for breakthrough pain. Parenteral oxycodone is a good alternative when opioids cannot be administered orally.

History

Opium contains two chemical classes of alkaloids, phenanthrenes and benzyl-isoquinolines. One of the phenanthrene alkaloids, thebaine, is extremely toxic and lacks analgesic properties. It is, however, an important precursor of several transformation products, including oxycodone.\(^13\)

Oxycodone was derived from thebaine in 1916\(^15\) and it was introduced into clinical practice in Germany in 1917.\(^1\) It was used in northern Europe mainly for acute pain. In Canada,
Australia, and the United States, it was used mainly as a combination drug with acetaminophen, phenacetin, and caffeine for moderate pain. In Finland, oxycodone has been used as the main parenteral opioid for acute pain since the 1960s.

Chemistry and Basic Pharmacology

The oxycodone (6-deoxy-7,8-dehydro-14-hydroxy-3-O-methyl-6-oxomorphine) molecule consists of two planar (A and B) and two aliphatic rings (C and D). Important groups for analgesic actions of the phenantrenes are linked to positions C3, C6, and N (Figure 1). Like morphine and methadone, oxycodone may exist in different enantiomers, but the biological effects of the putative isomers have not been studied.

Oxycodone has liposolubility similar to morphine, and both are significantly less lipid soluble than fentanyl. The respective partition coefficients of oxycodone and morphine are 0.7 and 0.5 or 1.7 and 1. The protein binding of oxycodone (44–46%) is close to that of morphine (38%) and it is not affected by α1-acid glycoprotein.

Oxycodone is a µ-opioid receptor specific ligand with clear agonist properties. The Ki (nM) of oxycodone for the µ-opioid receptor is 18 compared with 958 for the δ-opioid receptor and 677 for the κ-opioid receptor. The µ-opioid receptor binding affinity of oxycodone is, however, less than that of morphine or methadone. Oxymorphone, the active metabolite of oxycodone, has a significantly higher µ-opioid receptor binding affinity.

Intramuscular oxymorphone and morphine were compared in patients with chronic pain due to cancer. Intramuscular oxymorphone proved to be 8.7 times as potent as morphine in terms of total analgesic effect and 13 times as potent in terms of peak effect.

In behavioral studies in rats, oxycodone has been compared to morphine and has shown significantly weaker and briefer antinociception in the tail flick and hot plate tests after intrathecal (i.t.) and intracerebroventricular (i.c.v.) administration. After systemic administration (subcutaneous or intraperitoneal), oxycodone was shown to be 2–4 times more effective than morphine. These results have indicated that the active metabolites of oxycodone (e.g., oxymorphone) could be important in oxycodone-mediated analgesia. Studies using Dark Aguti rats that are deficient in the enzyme CYP2D1, which is required to O-demethylate oxycodone in the rat, and various opioid receptor antagonists have suggested that the antinociceptive effects of oxycodone could be κ-opioid receptor-mediated.

Pharmacokinetics

Healthy Volunteers. The metabolism of oxycodone in humans is still poorly characterized. The main known metabolic pathways of oxycodone are through O-demethylation to oxymorphone and via N-demethylation to noroxycodone. Noroxycodone concentrations in plasma and urine have been significantly higher after oral than after intramuscular administration, suggesting a prominent role of N-demethylation in the first-pass metabolism of oxycodone. The conversion of oxycodone to oxymorphone, and the conversion of noroxycodone to noroxymorphone, are catalyzed by the liver enzyme P450 2D6 (CYP 2D6). This enzyme has two phenotypes in the white population: 5–10% are poor metabolizers with diminished CYP 2D6 activity. Most of oxycodone and noroxycodone is excreted in urine as the free (unconjugated) form, whereas oxymorphone is mainly excreted in the conjugated form. The role of other metabolic routes such as N-oxidation and 6-ketoreduction in man have not been explored.
### Table 1: Pharmacokinetic Data of Oxycodone in Healthy Volunteers

<table>
<thead>
<tr>
<th>Drug and Dose (ref)</th>
<th>Tmax (h)</th>
<th>CL (L/min)</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR oxycodone 20 mg</td>
<td>80 ± 0.2</td>
<td>0.78 ± 0.2</td>
<td>0.46 ± 0.5</td>
</tr>
<tr>
<td>IRS oxycodone 20 mg</td>
<td>4.7 ± 2.5</td>
<td>0.78 ± 0.2</td>
<td>0.46 ± 0.5</td>
</tr>
<tr>
<td>IM oxycodone 0.14 mg/kg</td>
<td>2.6 (2.2–3.0)</td>
<td>0.78 (0.5–1.0)</td>
<td>0.46 ± 0.5</td>
</tr>
<tr>
<td>IV oxycodone 0.07 mg/kg</td>
<td>2.6 (2.2–3.1)</td>
<td>0.78 (0.5–1.0)</td>
<td>0.46 ± 0.5</td>
</tr>
</tbody>
</table>

Data on the pharmacokinetic parameters of oxycodone are shown in Table 1. The volume of distribution of oxycodone (2–3 L/kg) is comparable to that of morphine, but elimination is slower. The T1/2 is about 2–3 hours after i.v. administration, about 3 hours after immediate-release (IR) solution and about 8 hours after controlled-release (CR) oxycodone. The maximum plasma concentrations of oxycodone are reached within 25 min after i.v. administration and after 1.3 h and 2.6 h after IR and CR oxycodone, respectively. The maximum plasma concentrations of oxycodone after IR oxycodone are twice as high as those observed following an equivalent dose of CR oxycodone.

Kaiko et al. studied 28 healthy volunteers, half of whom were male. Both sexes were represented by 7 young and 7 elderly persons. Some interesting differences were observed. The absorption of oxycodone was greatest in elderly women and lowest in young men. The mean area under the curve (AUC) was 41% greater and the mean Cmax of oxycodone was 35% higher for women compared with men. On a weight-adjusted basis, women cleared oxycodone about 25% more slowly than men.

The main pharmacokinetic difference between oxycodone and morphine is in oral bioavailability. The bioavailability of oxycodone is >60% and the bioavailability of morphine is 20%.

### Kidney Failure

The bioavailability of 20 mg CR oxycodone was studied in 12 patients with creatinine clearance of 14–59 mL/min and in matched normal subjects with creatinine clearance values of 66–161 mL/min. Maximal oxycodone and noroxycodone concentrations were 50% and 20% higher in the patients with renal failure, respectively. The extent of absorption was 60%, 50%, and 40% greater for oxycodone, noroxycodone, and oxymorphone in renal failure. The T1/2 of oxycodone was one hour longer in renal failure.

The pharmacokinetics of i.v. oxycodone 0.07 mg/kg were studied in 10 uremic patients (mean serum creatinine concentration 644 ± 131 µmol/L) undergoing renal transplantation and ten healthy patients (mean serum creatinine concentration 72 ± 11 µmol/L) undergoing...
general surgery. The plasma concentrations of oxycodone and noroxycodone and the 24-hour urine recoveries of conjugated and unconjugated forms or oxycodone, noroxycodone, and oxymorphone were measured. The median $T_{1/2}$ of the uremic patients was prolonged to 3.9 h (1.8–25.7 h), compared with the patients who had normal renal function (median 2.3 h, range 1.3–4.0 h). This was due to increased volume of distribution and reduced clearance. The interindividual variation in uremic patients was great. Interestingly, the excretion of unconjugated oxycodone and noroxycodone in the urine was severely impaired in the uremic patients, whereas the excretion of conjugated forms was similar in both groups. Oxymorphone was excreted mainly in the conjugated form. However, the excretion of both conjugated and unconjugated forms was significantly reduced in uremic patients.

Liver Failure

Two studies have assessed the pharmacokinetics of oxycodone in hepatic impairment. Kaiko et al. compared the pharmacokinetics of a single dose of 20 mg CR oxycodone in 12 patients with hepatic impairment and 12 matched controls. The peak (Cmax) oxycodone concentrations were 40% higher and the AUC was 90% higher in hepatically impaired patients. The elimination ($T_{1/2}$) was prolonged by 2 hours. Consequently, oxymorphone concentrations were 15% (Cmax) and 50% (AUC) lower.

Tallgren et al. studied the pharmacokinetics of 0.05 mg of intravenous oxycodone in six patients with end-stage liver cirrhosis before and after liver transplantation. The median $T_{1/2}$ of oxycodone was 13.9 h (4.6–24.4 h) before transplantation and 3.4 h (2.6–5.1 h) after transplantation. Oxycodone clearance increased from 0.26 L/min to 1.13 L/min.

Pharmacokinetic Interactions

As oxycodone is metabolized in the liver by O-demethylation to form oxymorphone in a reaction catalyzed by the enzyme P450 2D6 (CYP 2D6), pharmacokinetic interactions that block CYP 2D6 can be anticipated. Because oxymorphone, the active metabolite, may be significant for oxycodone analgesia, one would expect a decrease in the efficacy or oxycodone in poor metabolizers and during coadministration with drugs that inhibit CYP 2D6. A case report suggested that fluoxetine hydrochloride, which is a potent CYP 2D6 inhibitor, increased the oxycodone requirement in a poor metabolizer.

Heiskanen et al. studied the role of oxymorphone in the pharmacodynamics of CR oxycodone in healthy volunteers by blocking the CYP 2D6 enzyme with quinidine. The metabolism of oxycodone to oxymorphone was almost completely blocked, with no significant changes on the pharmacodynamic effects. No painful stimuli were studied, however. The conclusion from that study was that at least in extensive CYP 2D6 metabolizers, the pharmacodynamic effects of a single dose of oxycodone are not dependent on oxymorphone.

Another type of interaction with SSRI antidepressants and oxycodone has been reported. Opioids can increase central serotonin levels, which would explain the serotonin syndrome reported with the coadministration of oxycodone and sertraline. The effects of four-day pretreatment with amitriptyline 25 mg on the pharmacokinetics and pharmacodynamics of a single dose oral oxycodone were studied by Pöyhä et al. No significant effects were found. Patients taking cyclosporine have been reported to be at a risk for pharmacokinetic drug interactions when cyclosporine has been used in combination with oxycodone.

Parenteral morphine has reduced the bioavailability of ciprofloxacin by up to 50%. No pharmacokinetic interaction seems to take place between another quinolone, levofloxacin, and a low dose of oral oxycodone 5 mg.

Pharmacodynamics

Studies in Healthy Volunteers. The standard psychomotor tests have been used to assess the pharmacodynamic effects of oxycodone in healthy volunteers. These tests include the digit symbol substitution test (DSST), which measures processing of sensory information; the critical flicker fusion test (CFF), which measures non-specific cortical arousal; pupilary
diameter and the Maddox wing test, which measures the central co-ordination of extraocular muscles.  

Oral IR oxycodone solution 0.28 mg/kg impaired the psychomotor function of volunteers, with a maximum effect at 1 hour. The cognitive skills were impaired for 4.5–5 h. Oxycodone also significantly decreased heart rate, had no significant effect on arterial blood pressure, and caused a significant increase in serum prolactin levels and a significant decrease in S-cortisol levels.

A drug effect questionnaire has also been used to assess the pharmacodynamics of oxycodone. The pharmacodynamic effects that showed a significant correlation with plasma concentrations of oxycodone were the following (correlation coefficient in parenthesis): pupil size (–0.53), sedation (0.43), respiratory rate (–0.33), and mood (–0.24). The subjects’ own estimations of the effects were: drug effect (0.57), sleepiness (0.42), dizziness (0.35), intoxication (0.33), nausea (0.28), energy level (0.27), relaxation (0.23) and itchiness (0.20). The observers assessed the subjects as having a drug effect (0.55), being relaxed (0.20), restless (–0.20), perspiring (0.18), drunk (0.17), talkative (0.16), vomiting (0.14), or scratching (0.10).

**Efficacy in Acute Postoperative Pain**

Parenteral oxycodone has been used for decades as the primary opioid analgesic for postoperative pain in Finland. Two clinical studies have compared i.v. oxycodone and morphine in acute postoperative pain.

In a randomized, double-blind study, Kalso et al. gave oxycodone or morphine in doses of 0.05 mg/kg i.v. after major abdominal surgery to 39 patients. The dosing interval was every 5 min until the patient did not want any further analgesics. Thereafter, the need for further doses was assessed every 15 min until the patient requested a dose, after which the patients was interviewed every 5 min until the next state of pain relief was reached. Significantly less oxycodone was needed than morphine, both to achieve the “first state of pain relief” (13.2 mg vs. 24.9 mg) and during the whole 2-hour study period (21.8 mg vs. 34.2 mg). The “first state of pain relief” was achieved faster (28 min vs. 46 min) and lasted longer (39 min vs. 27 min) with oxycodone than morphine. Morphine caused more sedation and greater decreases in the mean arterial blood pressure than oxycodone. In other respects, the two opioids were comparable.

The second study by Silvasti et al. used i.v. PCA with bolus doses of morphine 45 µg/kg and oxycodone 30 µg/kg in a randomized study after plastic reconstruction of the breast or major back surgery. The same amount of morphine and oxycodone was consumed by the patients during the 24-hour study. There was no difference in the quality of analgesia or incidence of adverse effects between oxycodone and morphine.

A third study compared i.v. PCA oxycodone with i.v. PCA tramadol in a prospective, double-blind, randomized study involving 54 patients after maxillofacial surgery. All patients were given diclofenac sodium 1 mg/kg intramuscularly and dexamethasone 8 mg twice a day. The oxycodone bolus was set at 0.03 mg/kg and that of tramadol was ten-fold higher, the lockout-time was 5 min. Pain was assessed at rest and during activity (mouth opening) before and after loading, at 2 h after commencing the PCA, as well as once in the evening and the following morning. Adverse effects were recorded. The equianalgesic dose ratio of tramadol to oxycodone was found to be approximately 8:1. There was no significant difference between the groups in pain intensity. No respiratory depression was identified. The incidence of nausea was slightly greater in the tramadol group than in the oxycodone group (44% vs. 28%, ns).

Controlled-release (CR) opioids have been introduced to postoperative pain management. CR oxycodone and morphine were compared in 154 patients with moderate to severe pain following abdominal hysterectomy. Either CR oxycodone 20 mg or 40 mg or CR morphine 45 mg or 90 mg was given as a single dose in a randomized, double-blind design. The total effect of CR oxycodone was about 1.8 times (95%CI: 1.09–2.42) more potent than CR morphine and 2.2 times (95% CI: 0.96–4.59) more potent for peak effect for equivalent doses. Time to peak pain relief was about 1 hour shorter with the higher dose of CR oxycodone (40 mg) compared with the higher dose of CR morphine (90 mg). Most patients reported onset of analgesia within 1 hour with
all doses. Adverse effects were similar with the two opioids.

The only published clinical study on spinal oxycodone is by Backlund et al., who compared epidural morphine and oxycodone in a randomized, double-blind study for pain after abdominal surgery. Thirty-three patients participated in the epidural part and a further 11 patients were given i.v. oxycodone in an open arm using the same dose of oxycodone that was given epidurally. Rescue medication was given with i.v. ketorolac and the rate of the epidural infusion was increased if needed. The initial doses for the boluses and infusions were based on a pilot study. The bolus for epidural morphine was 0.015 mg/kg followed by and infusion of 0.003 mg/kg/h, while the respective doses for oxycodone were ten times higher i.e. 0.15 mg/kg for the bolus and 0.03 mg/kg/h for the infusion. The final epidural dose ratio between morphine and oxycodone was 1:8.4–9.8 to provide comparable analgesia. During the infusion, the plasma concentrations of oxycodone were similar with i.v. and epidural administration. The results of this clinical study are in agreement with the reports on spinal administration of oxycodone in the rat. Efficacy in Cancer-Related Pain

The first controlled studies of oxycodone in cancer pain were performed by Beaver et al., These studies indicated that oxycodone could be a useful oral analgesic as it had a higher oral bioavailability than morphine. The first repeated dose cross-over studies comparing i.v. PCA and oral solution of oxycodone and morphine were performed by Kalso and Vainio and Kalso et al. These studies suggested that the oral bioavailability as calculated from daily consumption of each drug was 0.70 for oxycodone and 0.31 for morphine. The daily oral dose of oxycodone solution was suggested to be about 67% of that of morphine solution.

Controlled-release formulations of both oxycodone and morphine have made a major difference in the ease and simplicity of providing stable opioid analgesia in cancer pain. Both CR oxycodone and CR morphine provide, at proper doses, pain relief for 12 hours. The onset of analgesia is faster with CR oxycodone.

Three randomized and controlled studies have compared CR oxycodone and morphine. Two of these studies have used crossover designs, whereas one has been a parallel group study. A total of 177 patients were included in these studies and 73% completed the study protocol.

All studies suggest that both CR oxycodone and CR morphine provide adequate analgesia in moderate to severe cancer pain. The equianalgesic daily dose ratios of oxycodone:morphine vary from 3:4 to 1:2. The mean daily doses have been for CR oxycodone 148 ± 18 mg, 101 mg (40–360 mg), 93 ± 114 mg, and for CR morphine 204 ± 24 mg, 140 mg (60–300 mg), 145 ± 204 mg.

The adverse effects reported by the patients were typical opioid adverse effects, with no major differences between the groups. Fewer hallucinations were reported with oxycodone compared with morphine. Also less nausea and less pruritus have been reported with oxycodone compared with morphine. The crossover study design showed that for most patients the two opioids did not show much difference, whereas some individuals did significantly better on one or the other of the drugs. This study also suggested that there might be a period effect and that the efficacy and adverse effect profile of oxycodone could be different if oxycodone was started after long-term treatment on morphine.

The above-described studies lasted for about a week in each treatment arm. The long-term administration of CR oxycodone was studied by Citron et al. A total of 87 patients were included and 51% of the patients completed the 3-month study. A significant but modest increase in total daily CR oxycodone dose was seen. However, the percentage of patients reporting common opioid-related adverse effects decreased over the course of the study.

Efficacy in Chronic Non-Cancer Pain

Two randomized and placebo-controlled trials of CR oxycodone have been performed in osteoarthritis pain, one in postherpetic neuralgia (PHN), and one in diabetic polyneuropathy. Caldwell et al., enrolled 167 patients with osteoarthritis (OA), of whom one-third discontinued during the 30-day open titration period. One-fifth of the enrolled patients dropped out
because of adverse effects and a further 36 patients continued during the 30-day, double-blind, placebo-controlled, parallel group study. The mean dose at the end of titration was about 40 mg/day. Pain intensity decreased from 2.44 (0–3) to 1.38. The mean global pain intensity after 2 and 4 weeks of double-blind treatment was significantly lower on oxycodone than placebo. The pain intensity levels, however, tended to increase towards the end of the double-blind treatment. The quality of sleep was significantly improved on oxycodone compared with placebo.

Roth et al.\textsuperscript{59} randomized 133 patients with OA to double-blind treatment in parallel groups receiving either placebo, CR oxycodone 10 mg \times 2 or 20 mg \times 2 for 14 days. About 60\% of the patients had previously taken opioids and 65\% continued taking NSAIDs. Of the enrolled patients, 106 continued in an open-label extension trial for 6 months. A total of 58 patients completed 6 months, 41 completed a year, and 15 completed 18 months. Constipation, nausea, vomiting, somnolence, and pruritus were the most common adverse effects leading to discontinuation. CR oxycodone 40 mg per day reduced pain intensity on the average from a mean of 2.5 (0–3) to 1.5. The pain relief was significant compared with placebo. Pain relief was accompanied with more enjoyment of life, improved mood, and quality of sleep. The lower dose of CR oxycodone 20 mg/day was ineffective.

Fifty patients with PHN were recruited and 38 completed the placebo-controlled, crossover study of 4 weeks' duration in both arms.\textsuperscript{60} One-third of the patients continued with antidepressant therapy and 45\% of the patients had previously taken opioids for their PHN. The mean final dose of CR oxycodone was 45 \pm 17 mg. The maximum allowed dose would have been 60 mg per day. Compared with placebo, oxycodone resulted in significantly better pain relief (2.9 \pm 1.2 vs 1.8 \pm 1.1 on a scale from 0 to 5) and significant reductions in steady pain, allodynia, and paroxysmal spontaneous pain. Constipation (5\%), nausea (4\%), and sedation (3\%) were the most frequently reported adverse effect. Five patients discontinued while on oxycodone because of adverse effects.

Forty-five patients with diabetic neuropathy with at least moderate pain for at least 3 months were studied in an active placebo (benztropine), controlled, double-blind, crossover study. Each treatment arm lasted 4 weeks. The dose of CR oxycodone was titrated to a maximum possible of 80 mg/day. Thirty-six patients were evaluable. The mean daily dose for the last week of treatment was 40.0 \pm 18.5 mg of CR oxycodone. Mean daily pain intensity measured on a visual analogue scale was significantly lower with CR oxycodone (21.8 \pm 20.7) compared with the active placebo (48.9 \pm 26.6). Steady pain, “skin pain,” total pain, and disability were significantly improved on oxycodone compared with benztropine. Also sleep and some aspects of quality of life were significantly improved with CR oxycodone compared with placebo. Seven patients withdrew because of adverse effects (nausea, constipation, dizziness, and sweating) while receiving CR oxycodone and one on placebo. One patient suffered severe withdrawal symptoms during the washout period.

These data indicate that CR oxycodone provides significant pain relief in osteoarthritis-related pain and also in neuropathic pain due to postherpetic neuralgia or diabetic neuropathy. Adverse effects lead to treatment discontinuation in 10–30\% of the patients. The data so far are based on a selected group of patients and the studies are of a few weeks duration only.

\textbf{Morphine or Oxycodone?}

Both morphine and oxycodone provide effective analgesia in acute and chronic pain. Oxycodone has a more favorable pharmacokinetic profile. Its oral bioavailability is significantly higher and therefore the interindividual variation in bioavailability and expected plasma concentrations is less. Both drugs cause typical opioid-related adverse effects. However, several reports indicate that oxycodone causes fewer hallucinations.\textsuperscript{,5,8,55} Less itching with oxycodone\textsuperscript{55} may be related to the fact that oxycodone releases significantly less histamine than morphine.\textsuperscript{9} Oxycodone is not particularly effective when administered epidurally, whereas morphine has a powerful spinal analgesic effect.\textsuperscript{7,15,20}

\textbf{Current Controversies and Future Research}

The role of CYP 2D6 (genes and interactions) in the total analgesia of oxycodone still needs
to be clarified. After single dosing in extensive metabolizers, oxymorphone does not seem to be important for the psychomotor functions and other measures that have been assessed in healthy volunteers. However, the effects of blocking CYP 2D6 on pain relief and on repeated administration and particularly in poor metabolizers needs to be studied further.

Oxycodone has been suggested to be a κ-opioid receptor agonist. This is not likely as oxycodone is clearly a μ-opioid receptor agonist in receptor binding assays. More importantly, the pharmacodynamic effects of oxycodone in the human being are not those of a κ-opioid receptor agonist. Controlled trials are needed on the effects of rotating or switching from one opioid to the other. Also, suggestions that oxycodone and morphine show synergistic potentiation need to be confirmed in the clinic. This, however, requires a well designed study with a large number of patients. Animal studies indicate that morphine may display important immunosuppressive effects whereas oxycodone does not. The clinical relevance of this putative difference needs to be studied in patients.

References


